IBMPFD: *VCP* Animal Models

A *Drosophila* VCP (ter94) loss-of-function mutant has been identified as a dominant suppressor of expanded polyglutamine (poly-Q)-induced neuronal degeneration. This suggests that a gene dosage response for VCP expression is crucial to its function in expanded polyglutamine (poly-Q)-induced neuronal degeneration. To further support this, in transgenic *Drosophila*, in which VCP levels were elevated, severe apoptotic cell death was induced, whereas homozygous VCP loss-of-function mutants were embryonically lethal [Hirabayashi et al 2001].

A homozygous knock-out mouse model for VCP was embryonically lethal, the heterozygotes apparently being asymptomatic [Muller et al 2007]. Heterozygous p97+/- mice were indistinguishable from their wild-type littermates, whereas homozygous mutants did not survive to birth and died at a peri-implantation stage. These results show that p97 is an essential gene for early mouse development. Weihl et al [2007] reported their transgenic mice expressing p97/VCP-WT or the most common IBMPFD mutant, p97/VCP Arg155His, under a muscle-specific promoter. The latter became progressively weaker starting at age six months, a finding that coincided with abnormal muscle pathology including coarse internal architecture, vacuolation, and disorganized membrane morphology with reduced caveolin-3 expression at the sarcolemma. There was an increase in ubiquitin-containing protein inclusions and high molecular-weight ubiquitinated proteins, markers of ubiquitin-proteasome system (UPS) dysfunction.

References

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